Glycogen storage disease as a unifying mechanism of disease in the PRKAG2 cardiac syndrome

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Abstract

The AMP-activated protein kinase (AMPK) system was first discovered 30 years ago. Since that time, knowledge of the diverse physiological functions of AMPK has grown rapidly and continues to evolve. Most recently, the observation that spontaneously occurring genetic mutations in the γ regulatory subunits of AMPK give rise to a skeletal and cardiac muscle disease emphasizes the critical importance of AMPK in the maintenance of health and disease. The cardiac phenotype observed in humans harbouring genetic mutations in the γ2 regulatory subunit (PRKAG2) of AMPK is consistent with abnormal glycogen accumulation in the heart. The perturbation of AMPK activity induced by genetic mutations in PRKAG2 and the resultant effect on muscle cell glucose metabolism may be relevant to the issue of targeting AMPK in drug development for insulin-resistant diabetes mellitus.

Introduction

The AMP-activated protein kinase (AMPK) is known to regulate vital cellular metabolic cascades. A key function is the preservation of cellular ‘energy homoeostasis’ by the regulation of lipid and glucose metabolic pathways [1]. The α, γ and β subunits comprising AMPK are highly conserved through evolution [2]. Homologues for each subunit may be identified in fungi and plant species, reflecting the biological importance of AMPK in normal cellular physiology. A perturbation in the conserved physiological activity of AMPK, therefore, may, not surprisingly, result in consequences pathological to the cell.

Indeed, genetic mutations in γ regulatory subunits of AMPK have been identified in a breed of pigs and in humans, and have been shown to result in a pathological skeletal and heart muscle disease, respectively. The original identification of these genetic defects relied on the ‘genetic linking’ of the disease phenotype to a specific chromosomal region (locus) in the pig and human genome [3,4]. In each case, a gene encoding a γ regulatory subunit resided at the locus. Milan et al. [3] described a single base-pair (missense) mutation in the γ3 regulatory subunit of AMPK (PRKAG3) of the Hampshire pig, resulting in an amino acid change of arginine to glutamine at residue 200 (Arg-200Gln) in the protein [3]. Interestingly, the first human mutation identified occurred at the equivalent position in PRKAG2 (Arg-302Gln) [4]. Presently, six genetic mutations have been identified in the human PRKAG2 gene, giving rise to a complex cardiac syndrome [4–7]. This review will summarize the pathological features of the PRKAG2 cardiac syndrome and hypothesize a unifying mechanism of disease for this complex phenotype.

Disease phenotype in the PRKAG2 cardiac syndrome

In 1986, a novel familial cardiac syndrome was described in a large, non-consanguineous French–Canadian family [8]. Disease phenotype among affected family members was variable, and consisted of a triad of cardiac abnormalities. The clinical triad observed in patients, either alone or in combination, included ventricular pre-excitation [Wolff–Parkinson–White (WPW)], progressive conduction system disease and cardiac hypertrophy [9].

As the term implies, ventricular pre-excitation refers to early or ‘pre-excited’ electrical depolarization of ventricular myocardium before excitation would be expected to occur following conduction through the normal conduction pathway. The normal conduction axis of the heart, following sinus node depolarization in the right atrial chamber, proceeds via the atrio-ventricular node, where the electrical impulse is delayed before conducting to the ventricular chambers. This delay is visible on a 12-lead electrocardiogram in humans, showing distinct atrial and ventricular electrical activity. The pathological substrate for ventricular pre-excitation has been shown to be due to the existence of accessory conducting fibres that connect atrial and ventricular myocardium outside of the normal conduction axis of the heart. This condition is readily identified on 12-lead surface electrocardiograms of patients, which demonstrates merging of atrial and ventricular electrical signals. The presence of accessory conducting fibres provides a mechanism for episodes of ‘short-circuiting’ the heart, whereby electrical depolarization may follow a circular ‘re-entry’ pattern, utilizing both the normal conduction axis and the accessory conducting fibres. Circular re-entry leads to excessive heart rates, commonly in excess of 200 beats/min. The occurrence of episodic, rapid heart rates in the context of evidence for ventricular pre-excitation defines the WPW syndrome [10]. This clinical phenotype is frequently recognized during youth in patients with the PRKAG2...
cardiac syndrome and may be the sole manifestation of this genetic disease. Paradoxically, as patients reach their fourth decade of life, extremely slow heart rates may develop, suggesting a myopathic process affecting the accessory conducting fibres and the cells of the normal conduction axis of the heart, including the natural heart pacemaker, the sinus node. Many patients will require artificial pacemaker devices to maintain a sustainable heart rate.

In addition to WPW and a progressive development of conduction system disease, a significant number of patients will be found to have abnormal thickening of ventricular myocardium, as detected by ultrasound imaging. This condition is commonly referred to as hypertrophic cardiomyopathy (HCM). The pathological term ‘hypertrophy’ refers to cellular enlargement. Thus, cardiac hypertrophy is the gross manifestation of enlargement of cardiac cells. In a paediatric population, HCM is most commonly caused by genetic metabolic disorders, with an excess of 30 such disorders having been described [11]. Myocyte enlargement in this setting reflects a defect in the specific metabolic pathway involved, leading to excessive cellular storage of materials, for example lipid or glycogen. In an adult population, the isolated phenotype of HCM is well-recognized to occur secondary to genetic defects in sarcomeric (contractile) proteins, inherited as an autosomal dominant disease known as familial HCM [12]. In this disease, the basis of cellular enlargement results from increased numbers of sarcomeric units and organelles. Thus although ultrasound imaging will detect cardiac hypertrophy, whether the condition is secondary to a metabolic storage disorder or classical familial HCM cannot be differentiated in the absence of tissue histology. In the PRKAG2 cardiac syndrome, the observed phenotype of cardiac hypertrophy is most likely secondary to the degree of abnormal glycogen storage in the heart.

**Linking disease phenotype, genetic defect and protein function**

Knowledge of the physiological role of AMPK in mammalian cells has surged over the past 10 years. Of the multitude of substrates for the kinase now known, it was never thought that AMPK subunits would be candidate genes for inducing hereditary cardiac disease. This is not surprising, given the vast number proteins expressed in cardiac tissue and the rather widespread tissue activity of AMPK.

Ideally, the triad of pathology observed in the PRKAG2 cardiac syndrome should be explained by a single dominant cellular abnormality resulting from a perturbation in AMPK activity. The alternative approach is to invoke separate mechanisms for the diverse phenotype, a daunting task given the multiple cellular cascades that AMPK may influence. Therefore, the following hypothesis is an attempt to unify the observed clinical phenotype in this genetic syndrome with a single cellular pathology induced by altered AMPK muscle activity. However, it is important to recognize that variable expression of disease occurs in the PRKAG2 cardiac syndrome, which may be influenced by environmental and/or modifying genetic background factors.

The triad of clinical features described in the PRKAG2 cardiac syndrome strongly resembles the cardiac phenotype of a well-recognized metabolic storage disease, known as Pompe disease [13]. Pompe disease is an autosomal recessive genetic disorder caused by mutations in the gene encoding α-1,4-glucosidase [14]. The pathology of this disease is characterized by excessive cellular glycogen storage, resulting in severe organ hypertrophy [14]. Disease manifestation most commonly occurs in childhood. In the adult form, the clinical triad of WPW, progressive conduction system disease, and cardiac hypertrophy has been reported [15]. In light of the phenotypic similarity to a known glycogen storage disease, and the known role of AMPK in regulating the glucose metabolic pathway in muscle, focusing on abnormal glycogen storage as a unifying mechanism for disease pathology in the PRKAG2 cardiac syndrome appears reasonable.

First, it is necessary to hypothesize how abnormal cellular glycogen accumulation could manifest the observed clinical triad in patients with this genetic syndrome. In the context of cardiac hypertrophy, the explanation appears straightforward. The detection of abnormal myocardial thickening on ultrasound imaging is secondary to the enlargement (hypertrophy) of individual cardiac myocytes, as documented in known glycogen storage diseases [15,16]. The diagnosis of cardiac hypertrophy is based on conventional criteria defining normal myocardial wall thickness on imaging. Therefore, while some patients clearly exceed the defined criteria, others may not. However, it is likely that all patients with this syndrome exhibit some degree of abnormal cellular glycogen storage, the extent of accumulation defining the clinical diagnosis of cardiac hypertrophy.

The association of cardiac hypertrophy with WPW outside of the PRKAG2 cardiac syndrome and other storage diseases is a rare finding. How might abnormal glycogen accumulation in heart cells account for the pathological substrate of WPW, namely accessory conducting fibres outside of the normal conduction axis of the heart? A brief review of heart embryology may clarify this issue. During early cardiac development, the heart exists as a tubular structure with muscular continuity between atrial and ventricular myocardium [17]. Atrio-ventricular septation occurs between 7 and 12 weeks of fetal life, with myocardial continuity between atrial and ventricular myocardium now occurring primarily via the developed normal conduction axis [17]. However, it has been well established by histology study that remnants of atrio-ventricular muscle continuity outside of the normal conduction axis are still observed in normal fetal and neonatal hearts [17,18]. The observed accessory fibres connecting atrial and ventricular myocardium are thin in nature and would therefore not be expected to have the ‘cable’ capacity to conduct a depolarizing electrical wavefront from atrial to ventricular tissue. In this respect, these accessory fibres may be considered quiescent or subclinical and are a normal finding in newborn hearts. The effect
of glycogen accumulation may be postulated to promote conduction through these otherwise quiescent accessory fibres. First, the enlargement of these accessory fibres due to glycogen accumulation may improve their ‘cable’ capacity and ability to conduct a depolarizing waveform. This concept is consistent with the histological finding of abnormally enlarged accessory fibres, known to exist in normal hearts, giving rise to WPW in a patient with glycogen storage disease [13]. The effect of increased glycogen in myocytes may further alter electrical properties by other mechanisms. The relationship between decreased cellular pH due to glycogen accumulation [19] and the effect on myocyte conduction properties is unknown. However, given the known sensitivity of ion channel gating and current to intracellular pH [20,21], a change in kinetics favouring conduction would not be unexpected. The hypothesis presented to account for the presence of WPW in the PRKAG2 cardiac syndrome suggests that this phenotype is secondary to the effects of glycogen on naturally occurring, quiescent, accessory fibres. In this regard, implicating a specific, independent function of AMPK as a direct cause of this phenotype is not necessary.

A consistent feature of the PRKAG2 cardiac syndrome is the progressive development of slow heart rates, indicating loss of function of tissue in the normal conduction axis of the heart. In normal circumstances, the distribution of glycogen in the heart is known to exist to a greater extent in the specialized conduction tissue as compared with contracting myocardial cells [22]. Therefore, in the presence of a pathological condition leading to abnormal cellular glycogen storage, conduction tissue (sinus node, atrio-ventricular node) would not be excluded from the pathological consequences. Presumably, chronic accumulation and long-term exposure to high glycogen content exerts a degenerative and toxic effect on cells of the normal conduction axis (as well as on contracting myocytes), resulting in loss of function.

Biochemical and physiological studies presently support the hypothesis that the PRKAG2 cardiac syndrome represents a novel glycogen storage disease of the heart. Increased AMPK activity is observed in the presence of the equivalent Arg-302Gln mutation made by site-directed mutagenesis in the PRKAG1 isoform [23]. This increased activity appears to be independent of AMP levels and correlates with increased phosphorylation of acetyl-CoA carboxylase, a major substrate of AMPK [23]. These in vitro observations are of interest given that in vivo chronic activation of AMPK results in increased glycogen content of skeletal muscle in animal studies [24]. Consistent with this observation is the finding of increased GLUT4 transcript and membrane-bound protein levels in the presence of chronic AMPK activation [24,25]. More recent data suggest that the promotion of glycogen accumulation in muscle under chronic AMPK activation is due to enhanced glucose uptake, independent of AMPK’s effect of glycogen synthase or glycogen phosphorylase [26]. Thus, our current breadth of knowledge suggests that genetic defects in PRKAG2 may lead to increased AMPK activity, and the consequence of increased activity is abnormal glycogen accumulation in muscle. The fact that glycogen storage disease represents the pathology of the PRKAG2 cardiac syndrome is further supported by the recent data of Arad et al. [5].

Summary
Spontaneously occurring genetic mutations in the PRKAG2 subunit of AMPK cause a complex cardiac syndrome. This clinical syndrome is characterized by a triad of clinical disease, including WPW, progressive conduction system disease and cardiac hypertrophy. The expression of these phenotypes may be explained by abnormal glycogen accumulation within the heart, consistent with the known role of AMPK in regulating glucose metabolism. This rare genetic syndrome illustrates the critical role of AMPK in normal cellular physiology and demonstrates that a perturbation in the activity of AMPK may have pathological consequences. This concept is relevant to the targeting of AMPK in drug development for insulin-resistant diabetes mellitus [27], a condition with impaired muscle glucose uptake and glycogen stores. The altered AMPK activity due to genetic defects in the PRKAG2 cardiac syndrome may serve as a template in which to measure the appropriate effect and potency of new molecules in drug development.

References

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